Review

CONSTRICTION OF FETAL DUCTUS ARTERIOSUS AND MATERNAL INTAKE OF POLYPHENOL-RICH FOODS

Author:
Paulo Zielinsky

Fetal Cardiology Unit, Institute of Cardiology, Porto Alegre, Brazil

PRENAT CARDIO. 2014 DEC;4(4):6-18
DOI 10.12847/12141

Abstract

Fetal ductal constriction is a potentially severe functional alteration, often causing right ventricular overload and insufficiency, tricuspid regurgitation and neonatal pulmonary hypertension. Classically, maternal administration of indomethacin and/or other nonsteroidal antiinflammatory drugs interfere in prostaglandin metabolism, leading to ductal constriction. However, many cases of fetal ductal constriction, as well as of persistent neonatal pulmonary artery hypertension, remain without an established etiology, being referred as "idiopathic". In recent years, a growing body of evidences has shown that herbs, fruits, nuts, and a wide diversity of substances commonly used in daily diet, because of their high content of polyphenols, have definitive effects upon the metabolic pathway of inflammation, with consequent inhibition of prostaglandins synthesis. This anti-inflammatory action of polyphenols, when ingested during the third trimester of pregnancy, may interfere with the dynamics of fetal ductus arteriosus flow and cause ductal constriction. This review has the purpose to approach these new evidences, which may influence dietary orientation during pregnancy.

Key words: *ductal constriction, polyphenols, pulmonary hypertension, prostaglandins, antiinflammatory substances*

The ductus arteriosus originates from the distal portion of the left sixth aortic arch, which connects the left pulmonary artery to dorsal aorta [1]. Its histological structure is formed by an internal elastic membrane, a tunica media muscular layer and an external adventitial layer. The muscular layer is predominant, which makes the ductal structure different from aorta and pulmonary artery, and increases with gestational age. It has a circumferencial orientation, mainly at the external layers, which facilitates and makes effective ductal constriction [2].

How to Cite this Article:
Zielinsky P.: Constriction of fetal ductus arteriosus and maternal intake of polyphenol-rich foods. Prenat Cardio. 2014 Dec;4(4):6-18

The ductus arteriosus is positioned between the pulmonary artery, near the emergency of left pulmonary artery, and the aorta, at the zone of the isthmus. At the aortic-pulmonary plan, around 80-85% of the poorly saturated blood (50% oxygen) ejected by the right ventricle into the main pulmonary artery passes through the ductus arteriosus to the descending aorta (around 75 ml/min), and as a result will mix with the blood coming from the left ventricle. Due to the high pulmonary vascular resistance, only 15-20% (near 15 ml/min) are directed to the lungs. Around 40-50% of the descending aorta flow pass through the umbilical arteries and return to the placenta for the hematosis. The remaining blood will nourish the organs and the inferior body half [3].

The ductus arteriosus shows a peculiar differentiation program in order to prepare itself for postnatal spontaneous closure [1]. There is a relationship between gestational age and the histological maturation of the ductus [4]. The process of fetal intimal thickening starts at the second trimester of pregnancy and is characteristically a continuous process. This mechanism of intimal thickening seems to be linked to prostacyclin syntase (PGI2 syntase), which has a regulating role on ductal patency[5]. During ductus arteriosus closing there are higher PGI2 syntase levels in smooth muscle cells at the sites of intimal thickening than in other places. These findings demonstrate the relationship between ductal morphology and the presence of PGI2 syntase[6,7]. Vascular remodelling also seems to be associated to dedifferentiation of the smooth muscle cells and to apoptosis present in the areas of tunica media and intimal layers[8].

Hemodynamic alterations during the immediate neonatal period occur at the moment of cessation of placentary blood circulation, lung insuflation, pulmonary vasodilation and foramen ovale closure. The sudden increase in systemic vascular resistance and the decrease in pulmonary vascular resistance generate a reverse flow through the ductus arteriosus and an abrupt increase

Corresponding author: e-mail pesquisa@cardnet.tche.br or zielinsky@cardiol.br

Submitted: 2014-07-27; accepted: 2014-07-29

Figure 1. Ductus entering the descending aorta. 3D image in a 32 weeks normal fetus

in pulmonary flow. Some minutes after birth, 90% of the blood ejected by the right ventricle is directed to the pulmonary arteries. With the decrease in pulmonary vascular resistance there is an increase in pulmonary blood flow, which culminates with ductal occlusion[9,10]. The functional closure of ductus arteriosus is iniatiated by a mechanism induced by the higher blood oxygen concentration [11] . This mechanism, albeit mediated by prostaglandins and endothelins, is intrinsic to smooth muscle cells [12] . It is a potentially reversible phenomenon which occurs 8 -72 hours after birth, secondary to muscular constriction. After this event, there is a remodelling of the vascular wall, with neointimal formation caused by proliferation and migration of smooth muscle cells from the tunica media to the subentothelial layers. This seems to be the final event of a process which initiates at the second trimester of pregnancy, starting with the accumulation of glycosaminoglycans at the subendothelial region[5]. Usually, the ductus arteriosus remains patent for some hours or days in the neonatal period.

Physiological closure of the ductus in the term neonate starts with a phase of functional obliteration secondary to the wall vessel muscular constriction. The closure is gradual and is completed more frequently in 10 to 15 hours after birth[13]. Observations in neonates show that the arterial duct start to close at the pulmonary arterial end, and then the constriction spread to the aorta[14]. After completion of ductal occlusion, the arterial ligament is formed[15]. If the ductus arteriosus remains patent in a term neonate, this is considered a pathological condition. The premature baby shows a delay in the remodelling process of the tunica media layer and is less responsive to oxygen, probably as a result of the immaturity of the structures[16,17].

Since the ductus has a predominant muscular layer, its occlusion is influenced by a number of different constrictor and relaxing factors. Relaxing factors are prostaglandins, nitric oxide and bradycinin, which cause liberation of prostaglandins and nitris oxide. Constrictive factors are oxygen, high doses of bradycinin and autonomic nervous system, both sympathetic and parasympathetic[14]. The vasoconstrictive effect is dose-dependent to several neurotransmitters, such as **acetylcholine, histamine, serotonin and cathecolamins.** With the increase in gestational age, the ductus becomes less sensitive to the dilating effects and more sensitive to constrictive factor[14, 18, 19]. Production of prostaglandins is dependent of two enzymes which act in different states, cyclo-oxygenase-1 (COX-1), expressed endogenously, and cyclo-oxygenase-2 (COX-2), locally induced during inflammatory processes [7, 20].

Prostaglandins have been extensively studied, with clear demonstration of its potent vasodilating action upon the ductus arteriosus. However, in the last years new substances with constrictive and dilating effects on the ductus arteriosus have been described. The dilating action of 3- and 5-phosphodiesterase inhibitors upon fetal and neonatal ductus arteriosus in rodents have been reported[21,22]. This effect was shown to be more potent in fetuses than in neonates, suggesting that these substances could be useful in primary and secondary fetal ductal constriction, especially in preterm fetuses when compared to term fetuses[23]. Other substances with dilating effect on the ductus were described, based on the knowledge of the role of endothelin receptors as messengers of postnatal ductal constriction [9, 24, 25]. It was shown that antagonists of endothelin receptors cause potent in vitro inhibition of the constrictive effect of cyclo-oxygenase inhibitors during fetal life, and of the postnatal physiological ductal constriction induced by oxygen [26, 27] .

Among the substances with known constrictive effect upon the ductus arteriosus, **indomethacin,** a cyclo-oxygenase inhibitor used in the treatment of premature labor, is one of the most extensively studied 28-30 . Fetal ductal constriction may occur after few hours after maternal administration and its action may last for several weeks. For this reason, the absence of signs of ductal constriction after 24 to 72 hours of usage does not exclude the diagnosis [28, 29, 31-33]. Ductal sensitivity to indomethacin increases with gestational age, occurring in 5-10% of fetuses with less than 27 weeks, but reaching nearly 100 % after 34 weeks of gestation [34, 35] . In addition to indomethacin, it has been shown that several other **nonsteroidal anti-inflammatory drugs (NSAID), such**

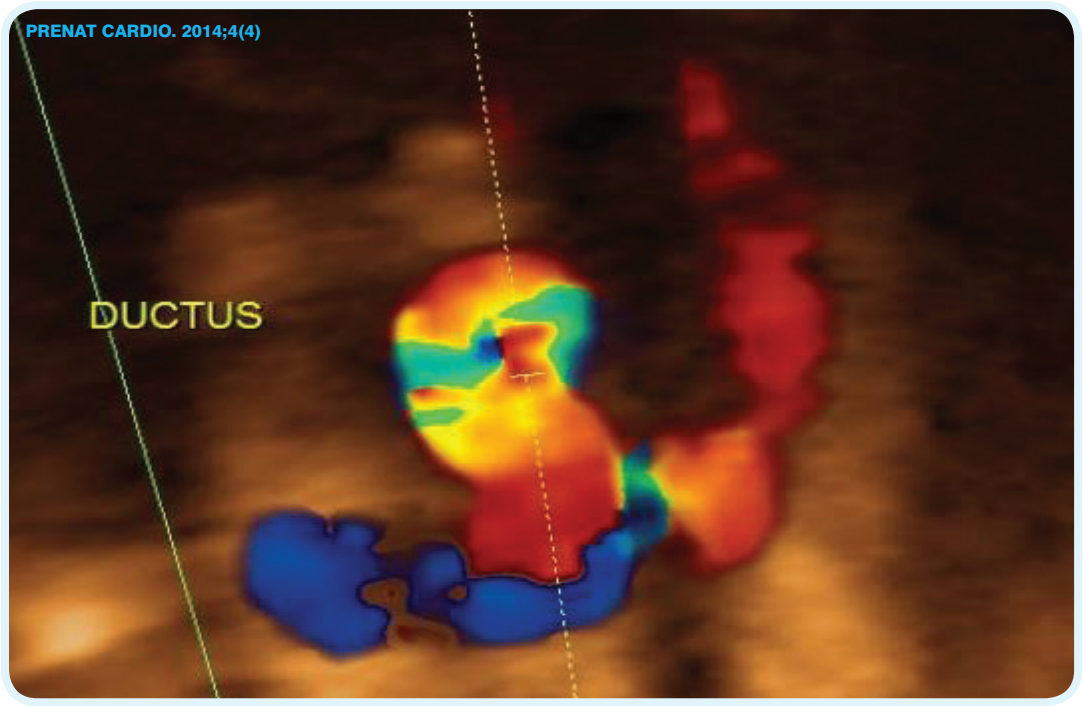

Figure 2. Ductal constriction. Color Doppler in a 33 weeks fetus exposed to a maternal polyphenol-rich diet. Notice the turbulent ductal flow.

as nimesulide [36], diclofenac[37], aspirin, matamizole, ibuprofen [38] and many others also have the potential to cause constriction of ductus arteriosus. Selective cyclo-oxygenase-2 inhibitors, such as rofecoxib[20,38,39], have also shown a constrictive ductal effect on rat and sheep fetuses[40-42]. **Sulindac,** another prostaglandin inhibitor drug utilized in premature labor, was demonstrated to have a milder and more transient constrictive effect on fetal ductus than indomethacin[33]. Glucocorticoids also show effects upon ductus arteriosus patency[43,44], but the pathophysiologic mechanism involved in the alteration of ductal tonus does not seem to be the same. There is apparent reduction in the ductal sensitivity to prostaglandin E2, which may be consequent to inhibition of the enzymatic liberation of arachidonic acid from phospholipids, a step in prostaglandin synthesis preceding cyclo-oxygenase[45]. Similar to other anti-inflammatory drugs, the ductal effect of glucocorticoid is dose-dependent[46]. Moreover, if associated to selective or non selective NSAID, glucocorticoid have a synergistic action which increase frequency and severity of ductal constriction; its incidence may double, possibly due to glucocorticoid ability to decrease the ductal sensitivity to prostaglandin[20, 30]. Other experimentally tested substances with proven constrictive action on rat fetuses are retinoic acid[20,30,34,47], antagonists of prostanoid EP4 receptors[21, 48, 49] and inhibitors of nitric oxide synthesis (L-name) [50-53], the latter with proven effects in humans. Recently, a novel mechanism for sustaining postnatal ductal constriction induced by oxygen has been described, based on ativation of the enzyme Rho-kinase[54].

The action of NSAID result from inhibition of prostaglandin synthesis, by inactivation of cyclo-oxygenases. COX-1 and COX-2 are enzymes involved in prostaglandin, prostacyclin and thromboxane biosynthesis [7]. This inhibitory mechanism interferes with the synthesis of prostaglandin G_2, which is a precursor of prostaglandin E_2eF$_2$[28,29]. The use of anti-inflammatory drugs during pregnancy for the treatment of premature labor, pre-eclampsia or intrauterine growth restriction through prostaglandin biosynthesis inhibition has allowed the study of the relation between ductal constriction and cyclo-oxygenase inhibitors. Indomethacin is the drug with prostaglandin inhibiting action most widely reported in the literature. Its inhibitor effect on cyclo-oxygenase is reversible, persisting until the drug is excreted[32,55]. The drug passage through the placentary barrier occurs freely during the second half of pregnancy, being minimal in early gestation[56]. The response to indomethacin is individual in each fetus, and even in a twin pregnancy only one fetus could be affected, which suggests differences in ductus maturation [57]. The ductus arteriosus becomes more sensitive to indomethacin as gestational age increases, ductal constriction occurring in 5-10% in fetuses with less than 27 weeks, 15-20% in fetuses between 27 and 31 weeks, 50% at the 32nd week and near 100% above 34 weeks. The occurrence of ductal constriction before the 27th week is uncommon, but there are reports of cases with 22 weeks[58].

As already mentioned, many other nosteroidal anti-inflammatory compunds beside intomethacin are potentially involved in ductal constriction, such as nimesulide[36], diclofenac [37], aspirin, metamizole, o ibuprofen[38], and others[59]. An experimental study in rats has suggested a gradation in the magnitude of the action of NSAID upon the fetal ductus, being the constrictive effect dose-dependent [60].

Glucocorticoids are synthetic hormones which mimic endogenous cortisol actions, a hormone produced by the glomerular zone of the adrenal gland. Glucocorticoids also act on ductal patency. As occurs with the majority of other anti-inflammatory substances, this effect is dose-dependent[46]. There is enymatic liberation of arachidonic acid, blocking prostaglandin synthesis[45], and apparent reduction in sinsitivity of the ductus to prostaglandin E_2. Despite the tendency to premature closure of ductus

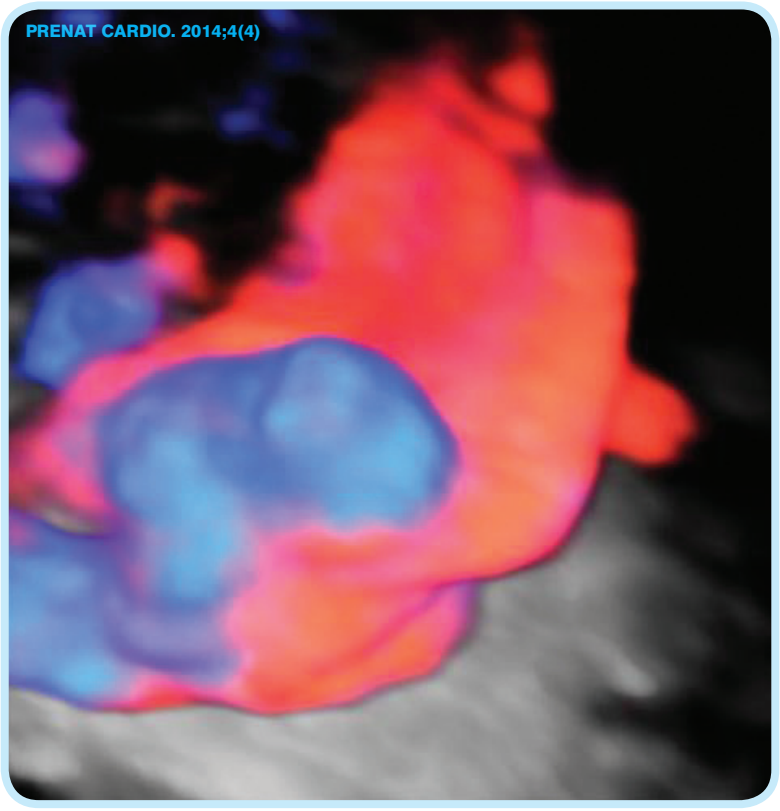

Figure 3. Ductal constriction. 3D image obtained with STIC of a tortuous and constricted ductus in a 29 weeks fetus.

arteriosus, the mechanism of action seems to be related to a primary alteration of the vessel, decreasing vascular reactivity to the relaxing effects of prostaglandin E_2, without altering its synthesis[40, 61]. The association of corticosteroids with indomethacin has shown a synergistic effect[62], and the incidence of ductal constriction doubles when these drugs are taken together, even though other studies have shown that the incidence of ductal constriction with glucocorticoid in isolation was similar to that of a control group[30].

Premature constriction of ductus arteriosus is followed by fetal hemodynamic repercussion. The higher resistance in the ductus generates blood flow turbulence, with increase in systolic and diastolic velocities and decrease in ductal pulsatility index. As a result, there is dilation of the pulmonary artery, right atrium and right ventricle, right to left bulging of the interventricular septum, tricuspid and pulmonary insufficiency and systolic and diastolic ventricular dysfunction [36, 63].

It has been demonstrated in a study in fetuses from 28 to 32 weeks of gestation after indomethacin administration that the drug shows a reversible constrictive effect on the ductus with significant reduction of pulsatility index and association with secondary disturbances, mainly in the right ventricle, as a result of the increase in afterload, observed after about 4 hours, and normalization 24 hours after withdrawl of the substance. It was suggested that the hemodynamic alterations secondary to ductal constriction are right ventricular dilation and signs of heart failure, followed by concentric hypertrophy, decrease in right ventricular chamber caused by mass increase and left ventricular compromise. These ventricular repercussions were more proeminent in the presence of tricuspid regurgitation[64, 65]. Flow redirected through the foramen ovale results in left chambers volumetric overload [65-67]. The aortic isthmus shows a rapid increase in its sectional area in response to local increased flow [68]. This redistribution keeps peripheral perfusion and may explain the findings from clinical experience that show that severe ductal constriction is well tolerated for some days in the human fetus.

Past experimental studies used to speculate that constriction of ductus arteriosus resulted in increase of the tunica media layer of pulmonary arteries and generates a secondary increase in intrauterine vascular pulmonary resistance [69]. The hemodynamic alterations in ductal constriction may be related to pulmonary vascular alterations. In the vast majority of studies directed to increase the knowledge about fetal and neonatal pulmonary arterial hypertension, fetal ductal constriction is the experimental model of choice. In a classical study, administration of indomethacin to fetal lambs was followed by fetal ductal constriction and pulmonary hypertension [70]. Blocking of prostaglandin biosynthesis has probably a direct effect in pulmonary arterioles in mammalian fetuses [71, 72]. The sustained increase in right ventricular afterload is capable to produce morphological, functional and hemodynamic modifications, with chronical histological and degenerative alterations of the right ventricular myocardium [73]. Severe ductal constriction may interfere in placentary flow and myocardial performance, and may lead to fetal death. If ductal constriction is less severe or chronical, fetal pulmonary arterial hypertension may be a consequence of excessive development of the arteriolar smooth muscular layer and constriction of the pulmonary arterioles. Predominance of the increased thickness of the muscular layer and of the aerial pathway mass is a feature less described in neonatal pulmonary hypertension consequent to other causes [74, 75]. In cases related to maternal drugs usage, ventricular dysfunction may reverse after its suspension. However, if this picture is not treated, it may be followed by endocardial ischemia and right ventricular papillary muscles dysfunction, and later on by heart failure, hydrops and potentially death [58]. Intrauterine ductal constrictiom may cause transient or permanent tricuspid regurgitation and neonatal myocardial ischemia [69, 76].

In clinical practice, in cases with severe ductal constriction after prostaglandin inhibitory drugs, the suspension of its usage may result in decrease of ductal velocities and increase in pulsatility index within 24 hours, with posterior normalization of hemodynamic consequences [55]. Mild cases may be approached with just

a decrease in the administred substance concentration, but in every fetus serial echocardiographic follow-up is reccomended [28].

The evidence of fetal cardiac dysfunction was described as a characteristic feature of fetal closure of ductus arteriosus [77]. In severe cases, interruption of pregnancy may be indicated, with neonatal cardiopulmonary ressucitation. The clinical course after birth depends on the severity of intrauterine right ventricular cardiac insufficiency and to the response to elevation in pulmonary vascular resistance [78].

Long term prognosis is still uncertain, but when early evolution is favorable, there are usually no late complications. After the occurrence of fetal heart failure, right ventricular functional abnormalities may persist throughout the neonatal period, even in those patients with a benign outcome.

Utilization of echocardiographic and Doppler techniques has allowed that the diagnosis of fetal ductal constriction, formerly possible only in necropsy, could be made in prenatal life [79]. Fetuses at risk for development of premature constriction of ductus arteriosus could be monitorized and submitted to early intervention when necessary.

Echocardiographic diagnosis of fetal ductal constriction is based on the presence, at color Doppler, of turbulent flow in the ductus with increased systolic velocity SV (higher than 1.4 m/s), increased diastolic velocity DV (higher than 0.30 m/s) and decreased pulsatility index PI (below 2.2). In the first publications, the cutoff point for the pulsatility index was described as 1.9 [80], but more recent studies have considered a somewhat higher limit[81, 82].The PI is independent of the ultrasound angle and is useful in the differential diagnosis when there is increased ductal flow without concomitant constriction. This situation may occur when the increased SV is caused by an increase in right ventricular output. The PI does not change with gestational age and should be used to define the diagnosis [83] (FIGURE 4). When there is total occlusion of the ductus arteriosus, absence of transductal flow is considered diagnostic. With the increase in afterload secondary to ductal constriction, the fetal heart shows initially proliferative growing and, at later stages, hyperplasia is substituted to apoptosis and hypertrophic response [84]. There is characteristically increase in right to left diametres ratio, an increase in pulmonary artery to aorta ratio and interventricular septum bulging toward the left ventricle [33].

Right ventricular systolic and diastolic function are impaired in fetuses with ductal constriction, assessed by different methods [73, 79, 85]. The hemodynamic compromise is considered mild when there is mild or no tricuspid and/or pulmonary regurgitation, with normal chambers diameters; moderate in the presence of tricuspid regurgitation with right ventricular dilation without hypertrophy and/or impaired contractility and severe when the tricuspid and/or pulmonary insufficiency is important or there is functional pulmonary atresia, right ventricular dilation with ventricular parietal hypertrophy and alteration in right ventricular contarctile function. The compromise is also considered severe when there is total ductal occlusion or, alternatively, in the presence of a PI lower than 1.0, associated to any degree of hemodynamic repercussion[23,79]. Since the constrictive effect upon the ductus arteriosus is predominantely dose-dependent[60], it is usual the resolution of hemodynamic alterations after suspension of the causing substances without development of fetal or neonatal cardiac dysfunction [33, 34, 86-88]. Even in the presence of a severe ductal constriction after maternal utilization of drugs with prostaglanin inhibiting effect, withdrawl of their use may show reversal of the increased SV and DV within 24 hours, with improvement of the hemodynamic alterations [33]. In some more severe cases, interruption of pregnancy may be necessary, sometimes with

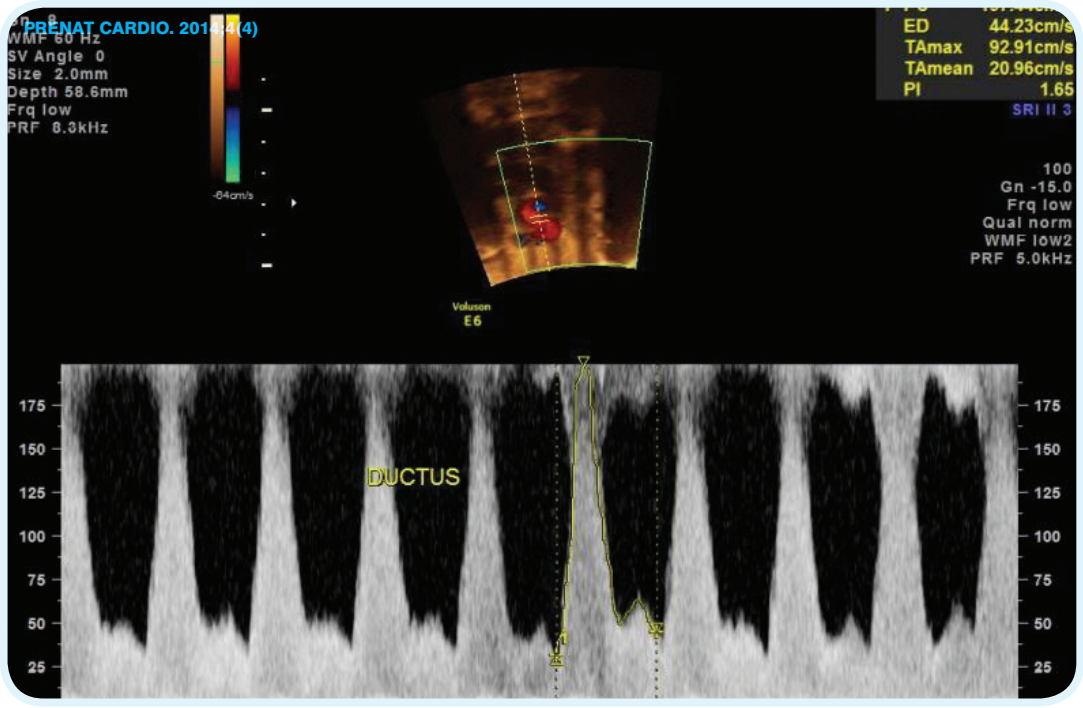

Figure 4. Pulsed Doppler tracing of a ductal flow in a 31 weeks fetus with constriction of DA caused by maternal ingestion of dark chocolate and grape juice. There is high systolic and diastolic peak velocities, as well as a decrease pulsatility index.

immediate cardiopulmonary neonatal ressucitation. Despite not having been established the association between duration of fetal ductal constriction and the prevalence and severity of neonatal pulmonary hypertension [19], it is obviously important to remove the cause as soon as possible, in order to allow early recovery.

The decision to interrupt pregnancy should take in account fetal pulmonary maturity, the severity of clinical and echocardiographic manifestations of ductal constriction and the presence or not of a progressive pattern. In the immediate neonatal period, the physiologic ductal closure associated to hemodynamic changes usual to this period allow normalization of the cardio-circulatory alterations secondary to the increased right ventricular overload. However, as already mentioned, the prolonged increase in right ventricular pressure, when transmitted to the lungs, may cause a reactive pulmonary arteriolar vasoconstriction with secondary pulmonary artery hypertension, which will need intensive treatment [89]. Since persi stent pulmonary hypertension of the neonate without cardiac abnormalities occurs in approximately 1/1000 liveborns, and around 23% of the cases do not have a known definitive etiology, very probably many of these cases are secondary to undetected fetal premature constriction of ductus arteriosus [90]. Thus, ductal constriction should always be considered an etiological possibility in "idiopathic" neonatal persistent pulmonary hypertension. This disorder carries a bad prognosis and is characterized by postnatal persistence of increased pulmonary vascular resistance, cyanosis due to right-to-left shunts through the foramen ovale and ductus, decreased pulmonary blood flow and severe hypoxemia [91, 92]. Persistent pulmonary hypertension of the newborn has been associated to antenatal exposure to NSAID [19, 93-102], even though a recent case-control study could not confirm this risk [103]. In fetal lambs, mechanical occlusion of the fetal ductus arteriosus reproduces the hemodynamic and structural features of persistent pulmonary hypertension of the newborn. Experimental prenatal exposition to NSAID has demonstrated alterations similar to those found in ductal constriction, with increased thickness of the smooth muscle layer of the pulmonary arterial vasculature [29, 104-106].

Polyphenols are chemical structures present in all the superior vegetal organisms. More than 8000 structures are known, and they act on pigmentation, growing, reproduction and resistance of plants against diseases[107]. There are flavonoid and non-flavonoid polyphenols.

Flavonoids represent the major family and are the basic structures of tannins or proanthocyanidins. Tannins and its flavonoids are the best known polyphenols in alimentation, because of their presence in **beer and wine,** but a wide variety of polyphenols are present in a great number of foods and beverages. Many studies have investigated the cynetic and extension of absortion of polyphenols by mensuration of plasma concentration and urinary or plasmatic excretion [108].

Flavonoids are the most abundant polyphenols in the human diet and its consumption has triggered the interest of consumers and food industries for many reasons, but mainly because of their biological activity in systems relevant to human health[109]. This biological activity is related to anti-inflammatory and antioxidant effects[110], based on its interference in the inflammatory cascade, with inhibition of prostaglandin synthesis and mediation of nitric oxide synthetase [111, 112].

Polyphenols with greater importance and literature references are catechins mainly in **green and black tea,** resveratrol in **wine and black grape**, chlorogenic acid in **coffee and teas** and flavonoids present in **fruits and vegetables** [113].

The principal alimentary sources with higher concentration in polyphenols are **herbal teas, mate tea, dark chocolate, fruits, natural juices, vegetables, olive and soy oils and red wine.** Among fruits, the highest concentration of flavonoids is orange, red and purple grape, strawberry and other berries, black prune and its derivatives. Vegetables with higher polyphenol purple onion concentration are purple onion, green spices, tomato and derivatives. These foods show a concentration above 30 mg of flavonoids per 100g of food, representing an amount above the 75th percentile of the USDA database [113].

In recent years, many investigational studies have been trying to ascertain the real therapeutic effect of substances found in nature and commonly used by general population. Several of these substances have nowadays their anti-inflammatory and antioxidant effects[114,115] scientifically and unequivocally demonstrated upon the chain of production of oxidative stress related to inflammatory mediators such as COX-2 and prostaglandin E2, metalproteinases and others. Substances rich in polyphenols are among the most widely used for a variety of reasons, even during pregnancy. The anti-inflammatory and antioxidant effects of these substances are secondary to inhibition of the metabolic route of prostaglandin, especially of cyclooxygenase-2, preventing the transformation of arachidonic acid into prostaglandin [20,39,59]. The literature reports on the mechanism of antioxidant and anti-inflammatory action of polyphenols, which are beneficial to a large portion of the population, and the scientific evidence of their ethnomedicinal effect, show that a large number of molecules derived from functional foods and plants have been isolated and even introduced successfully in the international pharmaceutical industry [116].

It has been demonstrated unambiguously that the polyphenols decrease oxidative stress (including in pregnancy) [117], plasma triglycerids and cholesterol levels [118], blood pressure[119, 120, 121], the consequences of gastric hypersecretion [122], the development of some neoplasms[123-125] and atherosclerosis[126, 127], the manifestations of aging [128] and Alzheimer's disease [129] and various other health problems. Polyphenols such as quercitin and kaempferol, among many others, are

present in many foods and their anti-inflammatory and antinociceptive activities have been shown to be as or more powerful than those of indomethacin [129-131].

Green tea, for example, is a compound of young leaves from the plant *Camellia sinensis* [132]. Approximately 30-40% of the leaves´ solid extract is composed of polyphenols, mainly catechins. Among the most important catechins present in green tea are epicatechin, gallate-3. epicatechin, epigallocatechin and, predominantely, gallate-3-epigallocatechin, with contains 7g per 100g of dry leaves. Several *in vitro* studies, both in animals and in humans, have demonstrated itheir antioxidant, anticarcinogenic, anti-inflammatory, probiotic and antimicrobial *actions secondary to inhibition of endogenous inflammatory response, dependent on the interference on the prostaglandin synthesis pathway* [133-136]. Black tea has also showed to be rich in catechins, and the tea compound envolving theaflavin has been shown to act on nitric oxide and on the liberation of arachidonic acid. It has already been clearly demonstrated that tea drinkers could benefit from the protective cardiovascular effects exerted by this polyphenol-rich substance [137, 138].

Resveratrol, a polyphenol compound found in grape rind, grape juice and red wine, is known by its antioxidant, antithrombotic anti-inflammatory and anticarcinogenic actions [139]. Several studies have demonstrated the effect of resveratrol upon the nervous system, as well as on the liver and the cardiovascular system. One of the possible mechanisms that explain its biological activity is related to a decrease in liberation of arachidonic acid, thus affecting induction of COX-2, with a consequent reduction in prostaglandin synthesis[140, 141].

Mate tea, a typical regional beverage very rich in polyphenols, widely consumed in South America, mainly Paraguay, Brazil, Argentina and Uruguay, is obtained from the dried and minced leaves of Ilex paraguariensis. Many studies have demonstrated its potent antineoplasic, anti-inflammatory and antioxidant effects, due to the action of its polyphenolic compounds[142].

Orange juice has been shown to have important antioxidant activity as a result of a high content of flavonoids, especially quercitin, and the ability of the phytochemical substance to interact with biomembranes. It was speculated that the daily consumption of orange juice might be useful in providing additional protection against cellular oxidation in vivo[143].

Dark chocolate shows high concentration of flavonoids and has anti-inflammatory properties. It has been demonstrated to have an inverse association with C-reactive protein, in amounts as low as 20g avery 3 days, suggesting that the regular intake of dark chocolate may reduce inflammatory processes[144]. Since flavonoids modify the production of pro-inflammatory cytokines, the synthesis of eycosanoids, the activation of platelets and nitric oxide-mediated mechanisms, a growing body of evidences are available to support a potent action of cocoa flavonoids in inflammation[145].

Many other substances rich in polyphenols present in nature commonly used in daily routine by the general population have also shown definite anti-inflammatory effects secondary to inhibition of the prostaglandin synthesis pathway. Examples are boldine, with anti-inflammatory and antithermic activities[146], propolis, with anti-inflammatory action in asthmatic patients[147], passion fruit, with cytotoxic, anti-inflammatory and scar-promoting effects[147-149], tomato and ginseng, also with anti-inflammatory action on COX-2[150] salvia, with anti-inflammatory effects on acute and chronic processes[151,152], chamomile, with moderate antioxidant and animicrobial activity and significant in vitro antiplatelet actions [153-155], and very many others, with variable concentrations of polyphenol substances presenting anti-inflammatory and antioxidant effects, all of them by interfering with prostaglandin synthesis.

A number of food and beverages such as herbal teas, grape and derivatives, orange, chocolate, fruits and many others, with high concentrations of polyphenols, are freely consumed throughout gestation. Despite the positive effects of polyphenols in general health, as discussed in the previous sections, other studies from our group ant others point toward the indication that maternal consumption of polyphenol-rich foods in late pregnancy, specifically in the third trimester, may be harmful to fetal health, as a result of the anti-inflammatory and antioxidant effects of these substances upon the ductus arteriosus, due to the inhibition of prostaglandin synthesis[81, 156-162].

Experimental studies to assess the fetal ductal effects of maternal consumption of polyphenol-rich foods utilized ewes in the last third of pregnancy (more than 120 days), corresponding to the third trimester of human gestation.

The fisrt study has shown that fetuses of ewes submitted to an **experimental diet of mate tea or green tea** as the only source of liquid for one week developped ductal constriction, with inequivocal histological signs: right ventricular enlargement, right ventricular hypertrophy and increased avascular zone thickness at the ductal wall[163].

The second study demonstrated that maternal exposure of green tea for one week was followed by fetal constriction**,** with increase in mean systolic velocity and mean diastolic velocity, decrease of pulsatility index and increase of mean right ventricular/left ventricular diameter ratio. Morphological repercussion was shown by dilated and hypertrophic right ventricles and increased ductal lumen avascular zone in the group exposed to green tea, but not in those of the control group, whose mothers have received only water[159].

A third experimental study, recently published[164], tested the hypothesis that maternal exposure to a diet with high content of polyphenols is followed by fetal ductal constriction and by alteration of endogenous inflammatory

and oxidant mediators. It was shown that an elevated experimental maternal polyphenol consumption in ewes induced fetal ductal constriction with increased urinary excretion of total polyphenols and alterations in biomarkers of oxidative stress, characterizing the antioxidant and anti-inflammatory actions of polyphenols [164, 165].

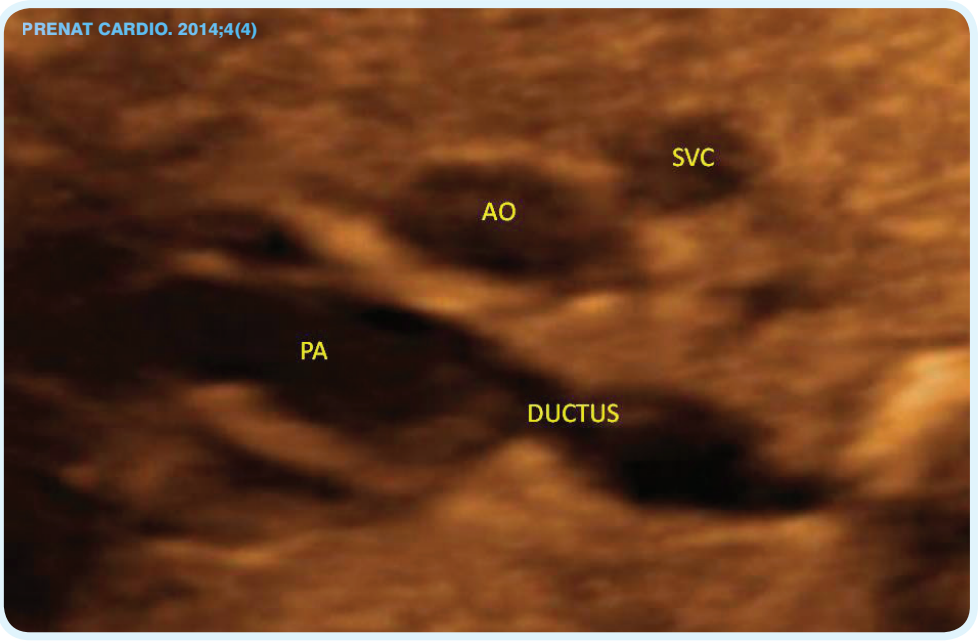

Figure 5. 2D three- vessels view of a 30 weeks fetus with ductal constriction. The pulmonary artery is larger than the aorta.

All clinical studies performed to evaluate the effects of maternal intake polyphenol-rich foods after the third trimester of pregnancy on fetal ductus arteriosus depend on the adequate assessment of its concentration, and there were no validated instruments to quantify total polyphenols in pregnant women. We showed the reproducibility and validity of a food frequency questionnaire (FFQ) with 52 items, to assess the intake of polyphenol-rich foods in pregnant women in Brazil[160].

In another study, we hypothesized that polyphenols or flavonoids present in food and beverages commonly consumed by pregnant women could influence ductal flow dynamics, probably by inhibition of prostaglandin synthesis, and thus be a risk factor for ductal constriction. With that in mind, we compared ductal flow behavior and right ventricular size in third-trimester fetuses exposed and not exposed to polyphenol-rich foods and beverages via maternal consumption. In a prospective analysis, Doppler ductal velocities and right-to-left ventricular dimensions ratio of normal fetuses exposed to polyphenol-rich foods (maternal consumption above the 75th percentile) were compared with normal unexposed fetuses (polyphenol ingestion below the 25th percentile). It was demonstrated that polyphenol-rich foods intake in late gestation triggers alterations in fetal ductal dynamics, since the exposed fetuses had significantly higher ductal flow velocities and increased right ventricles than not exposed fetuses[157].

We designed a study with the purpose to test the hypothesis that fetuses with constriction of ductus arteriosus and no history of maternal ingestion of NSAID, but whose mothers have used PRF in the third trimester, show reversal of the ductal constrictive effect and its hemodynamics consequences after maternal dietary intervention aimed at restriction of these substances. A controlled clinical trial of third trimester fetuses with ductal constriction with no history of NSAID intake was performed. All mothers were submitted to a food frequency questionnaire and were oriented to withdrawl polyphenol-rich foods, being reassessed after 3 weeks. Doppler parameters were assessed before and after discontinuation of these substances. A control group of third trimester normal fetuses, with no ductus arteriosus constriction, in which no dietary intervention was offered, was reviewed after 3 weeks. Ninety-six precent of the fetuses showed complete reversal of ductal constriction. In the control group, there was no significant differences in daily maternal consumption of PRF, ductal velocities, pulsatility index and right ventricular size. This behaviour is similar to that already widely reported upon the withdrawl of NSAID in fetuses with constriction of ductus arteriosus caused by those pharmacological agents, when there is habitual regression of the disorder. The original conclusion of this controlled clinical trial was that reduction of maternal polyphenol intake during pregnancy, especially in the third trimester, is followed by complete reversal of ductal constriction, which may reduce the risk of neonatal hypertension and influence maternal dietary habits in late pregnancy [81].

In a controlled clinical trial, we also demonstrated that, as already reported for fetuses with ductal constriction, dietary intervention for restricting for a period of two weeks or more the intake of foods rich in polyphenols by pregnant women in the third trimester also improves ductus arteriosus flow dynamics and decreases the right ventricle size in normal fetuses[156].

Other studies in the international literature have also discussed the relationship between idiopathic prenatal ductal constriction and maternal consumption of polyphenol-rich foods in late pregnancy, in the absence of exposure to nosnsteroidal antiinflammatory drugs[167,168]. Case reports have shown association of severe ductal constriction with hemodynamic repercussion (hydrops, enlarged right atrium and right ventricle) to maternal ingestion of polyphenols, such as violet vegetable juice, prune berry[169] and camomile herbal tea[162]. Kapadia, V., et al reported a case of fetal ductal cons-

triction related to maternal consumtion of a juice blend containing the cyclooxygenase and nitric oxide synthase inhibitors anthocyanins and proanthocyanidins for one week in late pregnancy. After birth, the newborn developped persistent neonatal pulmonary hypertension, needing oxygen for a prolonged period[161].

When the level of evidences regarding the reccomendation of avoidance of polyphenol-rich substances by pregnant women, at the third trimester, is critically analyzed, an important question naturally arises: why not to have performed or to perform a randomized clinical trial to obtain the strongest possible evidence of this action, at the apex of the pyramid? Such a study, in simple terms, would try to resolve the research problem of the value of nutritional intervention (restriction of polyphenols in maternal diet) against no intervention, in the presence of fetal ductal constriction without history of prenatal exposure to NSAID. In this hypothetical trial, the study factor would be the restriction of maternal intake of polyphenol-rich foods in fetuses with ductal constriction in late pregnancy and the outcome the improvement of fetal echocardiographic signs of ductal constriction - decrease is systolic and diastolic ductal velocities, increase in pulsatility index, decrease in right to left ventricular diameters ratio and pulmonary artery to aorta dimensions ratio, of flow turbulence, septal bulging and tricuspid regurgitation. Would there be equipoise in a randomized clinical trial with the proposed intervention and outcomes[170-174]? In other words, would it be ethical to perform a randomized clinical trial to assess the benefit of polyphenol restriction in maternal diet at the third trimester in the presence of ductal constriction? The answer to that question, considering the conceptual model to obtain a state of equipoise, is "no"! Such a state of equipoise needs the triangular interrelationship of the 3 points: 1) definite benefit of the study to society; 2) doubt of the investigator about the intervention effectivity; 3) safety of all the subjects in the two arms of the clinical trial[172,175-178]. Even though there is a clear benefit polyphenols in late pregnancy improves fetal ductal constriction, the two remaining points of the triangle of the conceptual model of equipoise are not fulfilled[179]. The uncertainty about the effectivity of maternal restriction of polyphenols is no longer present, based on the previous published studies herein disclosed and, most importantly, safety in the two arms of a randomized clinical trial in which one of them would not receive a clearly effective intervention can not be established. The deleterious effects of ductal constriction upon fetal henodynamics and the risk of pulmonary arterial hypertension secondary to this funcional disorder are well known. There are no reports in the literature of spontaneous reversal of ductal constriction, without removal of the causal factor. How to submit the control group to the risk of keeping the ducus constricted, with all its potential complications? In summary, a randomized clinical trial to assess the effect of maternal dietary intervention in fetuses with ductal constriction, with the level of evidences today accumulated, do not fulfill the equipoise principles, and for this reason can not be considered ethical.

The number of evidences already available recommend (Class IIa, level B) a note of caution with regard to the consumption by women in the third trimester of pregnancy of foods with high concentrations of polyphenols, as well as nonsteroidal antiinflammatory drugs, in order to avoid triggering constriction of ductus arteriosus, with its potential harmful consequences, such as fetal and neonatal heart failure and pulmonary arterial hypertension of the newborn.

All the information disclosed in this editorial has been discussed in a recently published review article[180].

References:

1. *Bergwerff M, DeRuiter MC and Gittenberger-de Groot AC.: Comparative anatomy and ontogeny of the ductus arteriosus, a vascular outsider. Anat Embryol (Berl) 1999, 200 (6): 559-71*
2. *Ho S.Y. and Anderson RH.: Anatomical closure of the ductus arteriosus: a study in 35 specimens. J Anat, 1979, 128 (Pt 4): 829-36*
3. *Yajima I, et al.: A subpopulation of smooth muscle cells, derived from melanocyte-competent precursors, prevents patent ductus arteriosus. PLoS One, 2013, 8 (1): e53183*
4. *Tada T, et al.: Human ductus arteriosus. A histological study on the relation between ductal maturation and gestational age. Acta Pathol Jpn 1985, 35 (1) : 23-34*
5. *Slomp J, et al.: Formation of intimal cushions in the ductus arteriosus as a model for vascular intimal thickening. An immunohistochemical study of changes in extracellular matrix components. Atherosclerosis 1992, 93 (1-2): 25-39*
6. *de Reeder EG, et al.: Distribution of prostacyclin synthase, 6-keto-prostaglandin F1 alpha, and 15-hydroxy-prostaglandin dehydrogenase in the normal and persistent ductus arteriosus of the dog. Am J Pathol 1989, 135 (5): 881-7*
7. *Majed BH, .: Molecular mechanisms regulating the vascular prostacyclin pathways and their adaptation during pregnancy and in the newborn. Pharmacological Reviews, 2012*
8. *Slomp J., et al.: Differentiation, dedifferentiation, and apoptosis of smooth muscle cells during the development of the human ductus arteriosus. Arterioscler Thromb Vasc Biol, 1997. 17(5): 1003-9*
9. *Hong Z., et al.: Role of dynamin-related protein 1 (Drp1)-mediated mitochondrial fission in oxygen sensing and constriction of the ductus arteriosus. Circ Res, 2013, 112 (5): 802-15*
10. *Obladen M.: History of the ductus arteriosus: 1. Anatomy and spontaneous closure. Neonatology 2011, 99 (2): 83-9*
11. *Coceani F.: Oxygen sensing in the ductus arteriosus: endothelin still a player. Circ Res 2013, 112 (11): e154*
12. *Michelakis ED, et al.,: Hypoxic pulmonary vasoconstriction: redox regulation of O2-sensitive K+ channels by a mitochondrial O2-sensor in resistance artery smooth muscle cells. J Mol Cell Cardiol 2004, 37 (6): 1119-36*
13. *Coceani F. and B. Baragatti.: Mechanisms for ductus arteriosus closure. Semin Perinatol 2012, 36 (2): 92-7*
14. *Heymann MA and Rudolph AM.: Control of the ductus arteriosus. Physiol Rev 1975, 55 (1): 62-78*
15. *Brezinka C, Gittenberger-de Groot AC and Wladimiroff JW.: The fetal ductus arteriosus, a review. Zentralbl Gynakol 1993, 115 (10): 423-32*
16. *Tynan M.: The ductus arteriosus and its closure. N Engl J Med 1993, 329 (21): 1570-2*
17. *Stoller JZ, et al.: Current Perspectives on Pathobiology of the Ductus Arteriosus. J Clin Exp Cardiolog 2001, 8(1)*

18. Levin M, et al.: ATP depletion and cell death in the neonatal lamb ductus arteriosus. Pediatr Res 2005, 57(6): 801-5

19. Tarcan A.: et al.: Persistent pulmonary hypertension in a premature newborn after 16 hours of antenatal indomethacin exposure. J Perinat Med, 2004. 32 (1): 98-9

20. Takami T, Momma K and Imamura S.: Increased constriction of the ductus arteriosus by dexamethasone, indomethacin, and rofecoxib in fetal rats. Circ J 2005, 69 (3): 354-8

21. Momma K, et al.: In vivo constriction of the fetal and neonatal ductus arteriosus by a prostanoid EP4-receptor antagonist in rats. Pediatr Res 2005, 58 (5): 971-5

22. Ichikawa Y, et al.: Inhibition of phosphodiesterase type 3 dilates the rat ductus arteriosus without inducing intimal thickening. Circ J, 2012, 76 (10): 2456-64

23. Toyoshima K., et al.: In vivo dilatation of the fetal and postnatal ductus arteriosus by inhibition of phosphodiesterase 3 in rats. Biol Neonate 2006, 89 (4): 251-6

24. Coceani F et al.: Deletion of the endothelin-A-receptor suppresses oxygen-induced constriction but not postnatal closure of the ductus arteriosus. J Cardiovasc Pharmacol, 2000. 36 (5 Suppl 1): S75-7

25. Baragatti B, et al.: Cytochrome P-450 3A13 and endothelin jointly mediate ductus arteriosus constriction to oxygen in mice. Am J Physiol Heart Circ Physiol 2011, 300 (3): H892-901

26. Momma KT, Nakanishi and Imamura S. .: Inhibition of in vivo constriction of fetal ductus arteriosus by endothelin receptor blockade in rats. Pediatr Res 2003, 53 (3): 479-85

27. Takizawa, T, et al.: Effects of TAK-044, a nonselective endothelin receptor antagonist, on the spontaneous and indomethacin- or methylene blue-induced constriction of the ductus arteriosus in rats. J Vet Med Sci 2000, 62 (5): 505-9

28. Norton ME.: Teratogen update: fetal effects of indomethacin administration during pregnancy. Teratology 199, 56 (4): 282-92

29. Sharpe GL, Larsson KS and Thalme B: Studies on closure of the ductus arteriosus. XII. In utero effect of indomethacin and sodium salicylate in rats and rabbits. Prostaglandins 1975, 9 (4): 585-96

30. Levy R, et al.: Indomethacin and corticosteroids: an additive constrictive effect on the fetal ductus arteriosus. Am J Perinatol 1999, 16 (8): 379-83

31. Dudley DK and Hardie MJ.: Fetal and neonatal effects of indomethacin used as a tocolytic agent. Am J Obstet Gynecol 1985, 151 (2): 181-4

32. Gordon MC and Samuels P.: Indomethacin. Clin Obstet Gynecol 1995, 38(4): 697-705

33. Rasanen J and Jouppila P.: Fetal cardiac function and ductus arteriosus during indomethacin and sulindac therapy for threatened preterm labor: a randomized study. Am J Obstet Gynecol 1995, 173 (1): 20-5

34. Moise KJ, Jr, et al.: Indomethacin in the treatment of premature labor. Effects on the fetal ductus arteriosus. N Engl J Med 1988, 319 (6): 327-31

35. Vermillion ST, et al.: The effect of indomethacin tocolysis on fetal ductus arteriosus constriction with advancing gestational age. Am J Obstet Gynecol 1997, 177 (2): 256-9

36. Paladini, D, Marasini M and Volpe P.: Severe ductal constriction in the third-trimester fetus following maternal self-medication with nimesulide. Ultrasound Obstet Gynecol 2005, 25 (4): 357-61

37. Auer M, et al.: Prenatal diagnosis of intrauterine premature closure of the ductus arteriosus following maternal diclofenac application. Ultrasound Obstet Gynecol 2004, 23 (5): 513-6

38. Schiessl B, et al.: Prenatal constriction of the fetal ductus arteriosus--related to maternal pain medication? Z Geburtshilfe Neonatol 2005, 209 (2): 65-8

39. Toyoshima K, et al.: Constriction of the ductus arteriosus by selective inhibition of cyclooxygenase-1 and -2 in near-term and preterm fetal rats. Prostaglandins Other Lipid Mediat 2006, 79 (1-2): 34-42

40. Clyman RI, et al.: Glucocorticoids alter the sensitivity of the lamb ductus arteriosus to prostaglandin E2. J Pediatr 1981, 98 (1): 126-8

41. Karadas B, et al.: Comparison of effects of cyclooxygenase inhibitors on myometrial contraction and constriction of ductus arteriosus in rats. Eur J Pharmacol 2004, 485 (1-3): 289-98

42. Takahashi Y, et al.: Cyclooxygenase-2 inhibitors constrict the fetal lamb ductus arteriosus both in vitro and in vivo. Am J Physiol Regul Integr Comp Physiol 2000, 278 (6): R1496-505

43. Clyman RI, et al.: Prenatal administration of betamethasone for prevention of patient ductus arteriosus. J Pediatr 1981, 98 (1): 123-6

44. Azancot-Benisty A, et al.: Constriction of the fetal ductus arteriosus during prenatal betamethasone therapy. Obstet Gynecol 1995, 85 (5 Pt 2): 874-6

45. Hassid A.: Regulation of prostaglandin biosynthesis in cultured cells. Am J Physiol 1982, 243 (5): C205-11

46. Momma K, Nishihara S, and Ota Y.: Constriction of the fetal ductus arteriosus by glucocorticoid hormones. Pediatr Res 1981, 15 (1): 19-21

47. Wu GR, et al.: The effect of vitamin A on contraction of the ductus arteriosus in fetal rat. Pediatr Res 2001, 49 (6): 747-54

48. Chen JX, et al.: Isoprostanes as physiological mediators of transition to newborn life: novel mechanisms regulating patency of the term and preterm ductus arteriosus. Pediatr Res 2012, 72 (2): 122-8

49. Fan F, et al.: Effect of PGE2 on DA tone by EP4 modulating Kv channels with different oxygen tension between preterm and term. International Journal of Cardiology, 2011 147:58-65, 2011

50. Keller RL, et al.: Combined treatment with a nonselective nitric oxide synthase inhibitor (l-NMMA) and indomethacin increases ductus constriction in extremely premature newborns. Pediatr Res 2005, 58 (6): 1216-21

51. Takizawa T, Kihara T and Kamata A.: Increased constriction of the ductus arteriosus with combined administration of indomethacin and L-NAME in fetal rats. Biol Neonate 2001, 80 (1): 64-7

52. Reese J, et.al.: Regulation of the fetal mouse ductus arteriosus is dependent on interaction of nitric oxide and COX enzymes in the ductal wall. Prostaglandins & Other Lipid Mediators 2009, 88: 89-96

53. Hsu JH, et al.: Nitric oxide alterations following acute ductal constriction in the fetal lamb: a role for superoxide. Am J Physiol Lung Cell Mol Physiol 2010, 298 (6): 880-7

54. Kajimoto H, et al.: Oxygen activates the Rho/Rho-kinase pathway and induces RhoB and ROCK-1 expression in human and rabbit ductus arteriosus by increasing mitochondria-derived reactive oxygen species: a newly recognized mechanism for sustaining ductal constriction. Circulation 2007, 115 (13): 1777-88

55. Vogel M, et.al.: Reversible ductus arteriosus constriction due to maternal indomethacin after fetal intervention for hypoplastic left heart syndrome with intact/restrictive atrial septum. Fetal Diagnosis and Therapy 2011, 27: 40-45

56. Moise KJ, Jr, et al.: Placental transfer of indomethacin in the human pregnancy. Am J Obstet Gynecol 1990, 162 (2): 549-54

57. Hallak M, et al.: Indomethacin for preterm labor: fetal toxicity in a dizygotic twin gestation. Obstet Gynecol 1991, 78 (5 Pt 2): 911-3

58. Moise KJ, Jr.: Effect of advancing gestational age on the frequency of fetal ductal constriction in association with maternal indomethacin use. Am J Obstet Gynecol 1993, 168 (5): 1350-3

59. Koren G, et al.: Nonsteroidal antiinflammatory drugs during third trimester and the risk of premature closure of the ductus arteriosus: a meta-analysis. Ann Pharmacother 2006, 40 (5): 824-9

60. Momma K, Hagiwara H and Konishi T.: Constriction of fetal ductus arteriosus by non-steroidal anti-inflammatory drugs: study of additional 34 drugs. Prostaglandins 1984, 28(4): 527-36

61. Cooper CL and Malik KU.: Effect of glucocorticoids on vascular reactivity to vasoactive hormones in rat isolated kidney: lack of relationship to prostaglandins. Br J Pharmacol 1984, 82 (3): 679-88

62. Wasserstrum N, et al.: Betamethasone and the human fetal ductus arteriosus. Obstet Gynecol 1989, 74(6): 897-900

63. Mushiake K, et. al.: Severe heart failure due to ductal constriction caused by maternal indomethacin. Pediatrics International 2002, 44:174-176,

64. Eronen M, et al.: The effects of indomethacin and a beta-sympathomimetic agent on the fetal ductus arteriosus during treatment of premature labor: a randomized double-blind study. Am J Obstet Gynecol 1991, 164 (1 Pt 1): 141-6

65. Eronen M.: The hemodynamic effects of antenatal indomethacin and a beta-sympathomimetic agent on the fetus and the newborn: a randomized study. Pediatr Res 1993, 33 (6): 615-9

66. Harlass FE, et al.: Hydrops fetalis and premature closure of the ductus arteriosus: a review. Obstet Gynecol Surv 1989, 44 (7): 541-3

67. Fyfe DA and Kline DC.: Fetal echocardiographic diagnosis of congenital heart disease. Pediatr Clin North Am 1990, 37 (1): 45-67

68. Momma K and Ando M.: In situ morphology of fetal aortic isthmus following ductal constriction in rats. Fetal Diagn Ther 1994, 9 (1): 53-61

69. Levin DL, et al.: Fetal hypertension and the development of increased pulmonary vascular smooth muscle: a possible mechanism for persistent pulmonary hypertension of the newborn infant. J Pediatr 1978, 92 (2): 265-9

70. Levin DL, Mills LJ and Weinberg AG.: Hemodynamic, pulmonary vascular, and myocardial abnormalities secondary to pharmacologic constriction of the fetal ductus arteriosus. A possible mechanism for persistent pulmonary hypertension and transient tricuspid insufficiency in the newborn infant. Circulation 1979, 60 (2): 360-4

71. Cassin S, et al.: Pulmonary and systemic vascular responses of perinatal goats to prostaglandins E1 and E2. Am J Physiol 1979, 236 (6): H828-32

72. Starling MB and Elliott RB.: The effects of prostaglandins, prostaglandin inhibitors, and oxygen on the closure of the ductus arteriosus, pulmonary arteries and umbilical vessels in vitro. Prostaglandins 1974, 8 (3): 187-203

73. Harada K, et al.: Doppler echocardiographic evaluation of ventricular diastolic filling in fetuses with ductal constriction. Am J Cardiol 1997, 79 (4): 442-6

74. Murphy JD, et al.: The structural basis of persistent pulmonary hypertension of the newborn infant. J Pediatr 1981, 98 (6): 962-7

75. Murphy JD, Vawter GF and Reid LM.: Pulmonary vascular disease in fatal meconium aspiration. J Pediatr 1984, 104 (5): 758-62

76. Levin DL, et al.: Morphological development of the pulmonary vascular bed in fetal lambs. Circulation 1976, 53 (1): 144-51

77. Macones GA and Robinson CA.: Is there justification for using indomethacin in preterm labor? An analysis of neonatal risks and benefits. Am J Obstet Gynecol 1997, 177 (4): 819-24

78. Hofstadler G, et al.: Spontaneous closure of the human fetal ductus arteriosus--A cause of fetal congestive heart failure. Am J Obstet Gynecol 1996, 174 (3): 879-83

79. Harada K, et al.: Two-dimensional echocardiographic evaluation of ventricular systolic function in human fetuses with ductal constriction. Ultrasound Obstet Gynecol 1997, 10 (4): 247-53

80. Huhta JC, et al.: Detection and quantitation of constriction of the fetal ductus arteriosus by Doppler echocardiography. Circulation 1987, 75 (2): 406-12

81. Zielinsky P, et al.: Reversal of fetal ductal constriction after maternal restriction of polyphenol-rich foods: an open clinical trial. J Perinatol 2012, 32 (8): 574-9

82. Mielke G and Benda N.: Reference ranges for two-dimensional echocardiographic examination of the fetal ductus arteriosus. Ultrasound Obstet Gynecol 2000, 15 (3) : 219-225

83. Tulzer G, et al.: Doppler echocardiography of fetal ductus arteriosus constriction versus increased right ventricular output. J Am Coll Cardiol 1991, 18 (2): 532-6

84. Van den Hoff MJ, et al.: Increased cardiac workload by closure of the ductus arteriosus leads to hypertrophy and apoptosis rather than to hyperplasia in the late fetal period. Naunyn Schmiedebergs Arch Pharmacol 2004, 370 (3): 193-202

85. Mori Y, et al.: Evaluation of systolic and diastolic ventricular performance of the right ventricle in fetuses with ductal constriction using the Doppler Tei index. Am J Cardiol, 2001. 88(10): 1173-8

86. Mari, G., et al.: Doppler assessment of the pulsatility index of the middle cerebral artery during constriction of the fetal ductus arteriosus after indomethacin therapy. Am J Obstet Gynecol, 1989. 161(6 Pt 1): 1528-31

87. Respondek M, Weil SR and Huhta JC.: Fetal echocardiography during indomethacin treatment. Ultrasound Obstet Gynecol 1995, 5 (2): 86-9

88. Rudolph AM.: The effects of nonsteroidal antiinflammatory compounds on fetal circulation and pulmonary function. Obstet Gynecol 1981, 58(5 Suppl): 63S-7S

89. Coceani F.: Control mechanisms for the ductus arteriosus and the perinatal pulmonary circulation. J Lipid Mediat 1993, 6 (1-3): 473-6

90. Van Marter LJ, et al.: Persistent pulmonary hypertension of the newborn and smoking and aspirin and nonsteroidal antiinflammatory drug consumption during pregnancy. Pediatrics, 1996, 97 (5): 658-63

91. Abman, SH.: Abnormal vasoreactivity in the pathophysiology of persistent pulmonary hypertension of the newborn. Pediatr Rev 1999, 20 (11): e103-9

92. Walsh-Sukys MC.: Persistent pulmonary hypertension of the newborn. The black box revisited. Clin Perinatol 1993, 20 (1): 127-43

93. Manchester D, Margolis HS and Sheldon RE.: Possible association between maternal indomethacin therapy and primary pulmonary hypertension of the newborn. Am J Obstet Gynecol 1976, 126 (4): 467-9

94. Csaba IF, Sulyok E and Ertl T.: Relationship of maternal treatment with indomethacin to persistence of fetal circulation syndrome. J Pediatr 1978, 92 (3): 484

95. Goudie BM and Dossetor JF.: Effect on the fetus of indomethacin given to suppress labour. Lancet 1979, 2 (8153): 1187-8

96. Rubaltelli FF, et al.: Effect on neonate of maternal treatment with indomethacin. J Pediatr 1979, 94 (1): 161

97. Besinger RE. et al.: Randomized comparative trial of indomethacin and ritodrine for the long-term treatment of preterm labor. Am J Obstet Gynecol 1991, 164 (4): 981-6 discussion 986-8

98. Wilkinson AR, Aynsley-Green A and Mitchell MD: Persistent pulmonary hypertension and abnormal prostaglandin E levels in preterm infants after maternal treatment with naproxen. Arch Dis Child 1979, 54 (12): 942-5

99. Turner GR and Levin DL.: Prostaglandin synthesis inhibition in persistent pulmonary hypertension of the newborn. Clin Perinatol 1984, 11(3): 581-9

100. Norton ME, et al.: Neonatal complications after the administration of indomethacin for preterm labor. N Engl J Med 1993, 329 (22): 1602-7

101. Alano MA, et al.: Analysis of nonsteroidal antiinflammatory drugs in meconium and its relation to persistent pulmonary hypertension of the newborn. Pediatrics 2001, 107 (3): 519-23

102. Hernández-Díaz S, et. al: Risk factors for persistent pulmonary hypertension of the newborn. Pedatrics 2007, 120:e272-

103. Van Marter LJ. et al.: Nonsteroidal antiinflammatory drugs in late pregnancy and persistent pulmonary hypertension of the newborn. Pediatrics 2013, 131 (1): 79-87

104. Heymann MA and Rudolph AM.: Effects of acetylsalicylic acid on the ductus arteriosus and circulation in fetal lambs in utero. Circ Res 1976, 38 (5): 418-22

105. Levin DL, et al.: Morphologic analysis of the pulmonary vascular bed in infants exposed in utero to prostaglandin synthetase inhibitors. J Pediatr 1978, 92 (3): 478-83

106. Lock JE, et al.: Indomethacin-induced pulmonary vasoconstriction in the conscious newborn lamb. Am J Physiol 1980, 238 (5): H639-51

107. Velioglu YS, et al.: Antioxidant activity and total phenolics in selected fruits, vegetables, and grain products. Journal of Agricultural and Food Chemistry 1998, 46:4113-4117

108. Bravo L.: Polyphenols: chemistry, dietary sources, metabolism, and nutritional significance. Nutr Rev 1998, 56 (11): 317-33

109. Scalbert A and Williamson G.: Dietary intake and bioavailability of polyphenols. J Nutr 2000, 130(8S Suppl): 2073S-85S

110. Majewska M, et al.: Evaluation of antioxidant potential of flavonoids: an in vitro study. Acta Pol Pharm 2011, 68(4): 611-5

111. Fukumoto LR and Mazza G.: Assessing antioxidant and prooxidant activities of phenolic compounds. J Agric Food Chem 2000, 48 (8): 3597-604

112. Nijveldt RJ, et al.: Flavonoids: a review of probable mechanisms of action and potential applications. Am J Clin Nutr 2001, 74 (4): 418-25

113. USDA, Database for the Flavonoid Content of Selected Foods Release

114. http://www.nal.usda.gov/fnic/foodcomp/Data/Flav/Flav02-1.pdf, 2007

115. Heijnen CG, et al.: Peroxynitrite scavenging of flavonoids: structure activity relations. Environ Toxicol Pharmacol 2001, 10 (4): 199-206

116. Chun OK, Kim DO and Lee CY.: Superoxide radical scavenging activity of the major polyphenols in fresh plums. J Agric Food Chem 2003, 51 (27): 8067-72

117. Akkol EK, et al.: The treatment of inflammation, pain, and Fever using medicinal plants. Adv Pharmacol Sci 2012, 2012: 476985

118. Chen B, et al.: Pomegranate juice and punicalagin attenuate oxidative stress and apoptosis in human placenta and in human placental trophoblasts. Am J Physiol Endocrinol Metab 2012, 302 (9): E1142-52

119. Andujar I, et al.: Cocoa polyphenols and their potential benefits for human health. Oxid Med Cell Longev 2012, 2012: 906252

120. Mathew AS, et al.: Acute effects of pomegranate extract on postprandial lipaemia, vascular function and blood pressure. Plant Foods Hum Nutr 2012, 67 (4): 351-7

121. Hodgson JM, et al.: Black tea lowers the rate of blood pressure variation: a randomized controlled trial. Am J Clin Nutr 2013, 97 (5): 943-50

122. Hodgson JM, et al.: Short-term effects of polyphenol-rich black tea on blood pressure in men and women. Food Funct 2013, 4 (1): 111-5

123. D'Argenio G, et al.: Apple polyphenol extracts prevent aspirin-induced damage to the rat gastric mucosa. Br J Nutr 2008, 100 (6): 1228-36

124. Khan HY, et al.: A prooxidant mechanism for the anticancer and chemopreventive properties of plant polyphenols. Curr Drug Targets 2012, 13 (14): 1738-49

125. Hadi SM, et al.: Oxidative breakage of cellular DNA by plant polyphenols: a putative mechanism for anticancer properties. Semin Cancer Biol 2007, 17 (5): 370-6

126. Malik A, et al.: DNA degradation by water extract of green tea in the presence of copper ions: implications for anticancer properties. Phytother Res 2003, 17 (4): 358-63

127. Widmer RJ, et al.: Beneficial effects of polyphenol-rich olive oil in patients with early atherosclerosis. Eur J Nutr 2013, 52 (3): 1223-31

128. Romain C, et al.: Vineatrol and cardiovascular disease: beneficial effects of a vine-shoot phenolic extract in a hamster atherosclerosis model. J Agric Food Chem 2012, 60 (44): 11029-36

129. Andrade JP and Assuncao M.: Protective effects of chronic green tea consumption on age-related neurodegeneration. Curr Pharm Des 2012, 18 (1): 4-14

130. Valls-Pedret C, et al.: Polyphenol-rich foods in the Mediterranean diet are associated with better cognitive function in elderly subjects at high cardiovascular risk. J Alzheimers Dis 2012, 29 (4): 773-82

131. Kupeli E, et al.: Estimation of antinociceptive and anti-inflammatory activity on Geranium pratense subsfinitimum and its phenolic compounds. J Ethnopharmacol 2007, 114 (2): 234-40

132. Kupeli E, et al.: Bioassay-guided isolation of anti-inflammatory and antinociceptive glycoterpenoids from the flowers of Verbascum lasianthum Boiss. ex Bentham. J Ethnopharmacol 2007, 110 (3): 444-50

133. Lorenzi HM, FJA.: Plantas medicinais no Brasil: nativas e exóticas. Nova Odessa: Instituto Plantarum de Estudo da Flora 2002: 512

134. Chen PC, et al.: A green tea-derived polyphenol, epigallocatechin-3-gallate, inhibits IkappaB kinase activation and IL-8 gene expression in respiratory epithelium. Inflammation 2002, 26 (5): 233-41

135. Di Paola R, et al.: Green tea polyphenol extract attenuates lung injury in experimental model of carrageenan-induced pleurisy in mice. Respir Res 2005, 6: 66

136. Smith DM and Dou QO.: Green tea polyphenol epigallocatechin inhibits DNA replication and consequently induces leukemia cell apoptosis. Int J Mol Med 2001, 7 (6): 645-52

137. Zhang G, Miura Y and Yagasaki K.: Suppression of adhesion and invasion of hepatoma cells in culture by tea compounds through antioxidative activity. Cancer Lett 2000, 159(2): 169-73

138. Duffy SJ, et al.: Short- and long-term black tea consumption reverses endothelial dysfunction in patients with coronary artery disease. Circulation 2001, 104 (2): 151-6

139. Duffy SJ, et al.: Effect of acute and chronic tea consumption on platelet aggregation in patients with coronary artery disease. Arterioscler Thromb Vasc Biol 2001, 21(6): 1084-9

140. Kris-Etherton PM, et al.: Bioactive compounds in foods: their role in the prevention of cardiovascular disease and cancer. Am J Med 2002, 113 Suppl 9B: 71S-88S

141. Martinez J and Moreno JJ.: Effect of resveratrol, a natural polyphenolic compound, on reactive oxygen species and prostaglandin production. Biochem Pharmacol 2000, 59 (7): 865-70

142. Subbaramaiah K, et al.: Resveratrol inhibits cyclooxygenase-2 transcription and activity in phorbol ester-treated human mammary epithelial cells. J Biol Chem 1998, 273 (34): 21875-82

143. Bixby M, et al.: Ilex paraguariensis extracts are potent inhibitors of nitrosative stress: a comparative study with green tea and wines using a protein nitration model and mammalian cell cytotoxicity. Life Sci 2005, 77 (3): 345-58

144. Ito H, et al.: Polyphenol levels in human urine after intake of six different polyphenol-rich beverages. Br J Nutr 2005, 94 (4): 500-9

145. Di Giuseppe R, et.al.: Regular consumption of dark chocolate is associated with low serum concentrations of C-reactive protein in a healthy Italian population. The Journal of Nutrition 2008, 138:1939-1945

146. Selmi C, et al.: Chocolate at heart: the anti-inflammatory impact of cocoa flavanols. Mol Nutr Food Res 2008, 52 (11): 1340-8

147. Backhouse N, et al.: Anti-inflammatory and antipyretic effects of boldine. Agents Actions 1994, 42 (3-4): 114-7

148. Khayyal MT, et al.: A clinical pharmacological study of the potential beneficial effects of a propolis food product as an adjuvant in asthmatic patients. Fundam Clin Pharmacol 2003. 17 (1): 93-102

149. Silva JR, et al.: Extract of Passiflora edulis in the healing process of gastric sutures in rats: a morphological and tensiometric study. Acta Cir Bras 2006, 21 Suppl 2: 52-60

150. Montanher AB, et al.: Evidence of anti-inflammatory effects of Passiflora edulis in an inflammation model. J Ethnopharmacol 2007, 109 (2): 281-8

151. Jin UH, et al.: Inhibitory effect of Panax notoginseng on nitric oxide synthase, cyclo-oxygenase-2 and neutrophil functions. Phytother Res 2007, 21 (2): 142-8

152. Bozin B, et al.: Antimicrobial and antioxidant properties of rosemary and sage (Rosmarinus officinalis L. and Salvia officinalis L., Lamiaceae) essential oils. J Agric Food Chem 2007, 55 (19): 7879-85

153. Celik I and Isik I.: Determination of chemopreventive role of Foeniculum vulgare and Salvia officinalis infusion on trichloroacetic acid-induced increased serum marker enzymes lipid peroxidation and antioxidative defense systems in rats. Nat Prod Res 2008, 22 (1): 66-75

154. Della Loggia R, et al.: The role of flavonoids in the antiinflammatory activity of Chamomilla recutita. Prog Clin Biol Res 1986, 213: 481-4

155. Pozharitskaya ON, et al.: Separation and evaluation of free radical-scavenging activity of phenol components of green, brown, and black leaves of Bergenia crassifolia by using HPTLC-DPPH method. J Sep Sci 2007, 30 (15): 2447-51*

156. Pozharitskaya ON, et al.: Separation and evaluation of free radical-scavenging activity of phenol components of Emblica officinalis extract by using an HPTLC-DPPH method. J Sep Sci 2007, 30 (9): 1250-4*

157. Zielinsky P, et al.: Maternal restriction of polyphenols and fetal ductal dynamics in normal pregnancy: an open clinical trial. Arq Bras Cardiol 2013, 101 (3): 217-225

158. Zielinsky P, et al.: Maternal consumption of polyphenol-rich foods in late pregnancy and fetal ductus arteriosus flow dynamics. J Perinatol 2010, 30 (1): 17-21

159. Zielinsky P, et al.: New insights on fetal ductal constriction: role of maternal ingestion of polyphenol-rich foods. Expert Rev Cardiovasc Ther 2010, 8 (2): 291-8

160. Zielinsky, P, et al.: Fetal ductal constriction caused by maternal ingestion of green tea in late pregnancy: an experimental study. Prenat Diagn 2012, 32 (10): 921-6

161. Vian I, et al.: Development and validation of a food frequency questionnaire for consumption of polyphenol-rich foods in pregnant women. Matern Child Nutr 2013 DOI10.III/mcn.I 2025

162. Kapadia V, et al.: Prenatal closure of the ductus arteriosus and maternal ingestion of anthocyanins. J Perinatol 2010, 30 (4): 291-4

163. Sridharan S, Archer N and Manning N.: Premature constriction of the fetal ductus arteriosus following the maternal consumption of camomile herbal tea. Ultrasound Obstet Gynecol 2009, 34 (3): 358-9

164. Zielinsky P, et al.: Experimental study of the role of maternal consumption of green tea, mate tea and grape juice on fetal ductal constriction. 17th World Congress on Ultrasound in Obstetrics and Gynecology 2007,Ultrasound in Obstetrics and Gynecology 2007, 30: 515

165. Bubols GB, et al.: Nitric oxide and reactive species are modulated in the polyphonol-induced ductus arteriosus constriction in pregnant sheep. Prenat Diagn 2014, doi: 10.1002/pd.4463

166. Zielinsky P, et al.: Experimental Assessment of Ductus Arteriosus Flow, Oxidative Stress and Polyphenol Excretion After Maternal Polyphenol-Rich Diet in Late Pregnancy. 22nd World Congress on Ultrasound in Obstetrics and Gynecology, 2012, Copenhagen - Ultrasound in Obstetrics and Gynecology 2012, 40: 16

167. Mercanti I, et al.: Ibubrofen in the treatment of patent ductus arteriosus in preterm infants: what we know, what we still do not know. Curr Pharm Des 2012, 18 (21): 3007-18

168. Shima Y, et al.: Idiopathic severe constriction of the fetal ductus arteriosus: a possible underestimated pathophysiology. Eur J Pediatr 2011, 170 (2): 237-40

169. Enzensberger C, et al.: Idiopathic constriction of the fetal ductus arteriosus: three cases and review of the literature. J Ultrasound Med 2012, 31 (8): 1285-91

170. Tanaka M, et al.: Functional foods for the fetus? Acta Obstet Gynecol Scand 2011, 90(10): 1172-3

171. Sheehan M, et al.: Position statement on ethics, equipoise and research on charged particle radiation therapy. J Med Ethics, 2013

172. Petticrew M, et al.: In search of social equipoise. BMJ 2013, 347: f4016

173. Freedman B.: Equipoise and the ethics of clinical research. N Engl J Med 1987, 317 (3): 141-5

174. Hellman S and Hellman DS.: Of mice but not men. Problems of the randomized clinical trial. N Engl J Med 1991, 324 (22): 1585-9

175. Joffe S and Miller FG.: Equipoise: asking the right questions for clinical trial design. Nat Rev Clin Oncol 2012, 9 (4): 230-5

176. Adibe OO and Peter SD.: Equipoise, ethics, and the necessity of randomized trials in surgery. Arch Surg 2012, 147 (10): 899-900

177. Gifford F.: Pulling the plug on clinical equipoise: a critique of Miller and Weijer. Kennedy Inst Ethics J 2007, 17 (3): 203-26; discussion 227-46

178. Van der Graaf R.: On what we will lose in giving up on clinical equipoise: A reply to Miller. Clinical Trials, 2012

179. Van der Graaf R.: Equipoise should be amended, not abandoned. Clinical Trials, 2011

180. Zielinsky P and Busato S.: Prenatal effects of maternal consumption of polyphenol-rich foods in late pregnancy upon fetal ductus arteriosus. Birth Defects Research (Part C) 2013. 99: 256–74

Conflict of interest

Author do not report any financial or personal links with other persons or organizations, which might affect negatively the content of this publication and/or claim authorship rights to this publication